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TOPICAL REVIEW

From gene action to reactive genomes

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Abstract Poised at a critical turning point in the history of genetics, recent work (e.g. in genomics, epigenetics, genomic plasticity) obliges us to critically reexamine many of our most basic concepts. For example, I argue that genomic research supports a radical transformation in our understanding of the genome – a shift from an earlier conception of that entity as an effectively static collection of active genes to that of a dynamic and reactive system dedicated to the context specific regulation of protein-coding sequences.

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Prelude

We've all heard the hype; we know that the discovery of epigenetic inheritance is upsetting our traditional understandings of genetics; 'Rocking the foundations of molecular genetics' (Mattick, 2012); resurrecting Lamarck; and teaching us 'How You Can Change Your Genes' (http://content.time.com/time/specials/packages/article/0,28804,1952062_1952061_1952056,00.html). Of course it is not all hype. Epigenetic inheritance does not teach us how to 'change our genes' (its primary effect is to alter patterns of gene expression), yet there is little doubt that its discovery and its integration into mainstream genetics is indeed rocking the foundations of that science, and it is doing so in ways that have enormous implications for our conceptual framing of its core questions about heredity, development, and evolution. My main worry is that this work is often presented in terms that undercut its most important and most radical implications. Epigenetic inheritance is not about a competition between 'extra'-, 'epi'-, or 'non'-genetic contributions to heredity and more traditionally genetic contributions. Rather, it challenges the very distinction between 'genetic' and 'non-genetic'. As such, it is part of a much larger revolution in our thinking both about the relation between genes, genomes, and organisms, and about the relation between all three of these entities and their environments.

Over a decade ago, the philosopher of biology James Griesemer (Griesemer, 2002) asked the crucial question: 'What is "Epi" about Epigenetics?', rightly observing that 'What counts as epigenetic depends on what counts as genetic' (p. 97). But Griesemer's concern is not so much with terminology as with the theoretical perspective of Weismannism that has dominated so much of our thinking in both classical genetics and, in the guise of the 'central dogma', in molecular biology as well. 'According to Weismannism,' he writes, 'all causality (other than that due to environments . . .) traces to germ or genes; the body or its phenotype is a causal dead end' (Griesemer, 2002). This perspective clearly places genetics both prior to and separable from development; it also, as he writes, structures 'our basic representations and models of what counts as genetic and, therefore, our basic representations of what counts as epigenetic.'

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Griesemer opts for a radical alternative: a theoretical perspective that places at its core not genes, genomes, or germ cells, but the fundamentally recursive ('chicken-and-egg') character of living systems. He suggests that the process of reproduction captures this essential recursivity. As he writes,

> reproduction is the multiplication of entities in such a way that the parts transferred to the off-spring confer on them the capacity to develop. And the capacity to develop is the capacity to acquire the capacity to reproduce.
>
> This is a recursive structure, and its recursiveness captures what I mean by saying that heredity and development are intertwined in reproduction processes. (pp. 105–106).

From this perspective, 'Inheritance is a special case of reproduction processes' and 'Genetic inheritance is a special case of inheritance.' Reproduction, life as we know it, requires some sort of inheritance system(s), but the transmission of genes is not itself a necessary prerequisite.

I am sympathetic. I too am persuaded that many of the problems with the traditional perspective derive from the core belief in the separation of genes from soma, of genetics from development, and I agree that what is needed is a theoretical perspective that replaces the linear causal structure that is supposed to take us from genotype to phenotype by one that incorporates both the fundamental circularity (or recursivity) of living systems and their *a priori* inseparability from the environments in which, and out of which, they take their form. I too ask, 'what is "epi" about epigenetics?', but I take a somewhat different route from that of Griesemer. Above all, I am inspired by the ways in which findings of molecular genomics – primarily over the dozen or so years since his paper – oblige us to rethink the very meaning of genetics. More specifically, my argument might be construed as extending his own critique down to the level of genetics itself, arguing not only for the ongoing interactivity between genetics and development but also for the inherent responsiveness of the genome itself. No longer does it make sense to think of the genome as a starting point, as the beginning of a causal chain that takes us from genotype to phenotype. Instead, I claim, we need to reconceptualize it as itself a fundamentally reactive system, a sub-system of the cell composed of DNA that has been designed over the course of evolution to sense and to respond to the signals impinging on it. The sequence of the genome's DNA determines both its sensitivity and its ability to respond to outside signals. This it does through changes in conformation, chromatin remodelling, methylation of the DNA – in short, through many of the mechanisms associated with epigenetic inheritance.

Barbara McClintock was one of the earliest to anticipate such a reformulation. In 1984, in the closing remarks of her Nobel Laureate speech, she described the genome 'as a highly sensitive organ of the cell that monitors genomic activities and corrects common errors, senses unusual and unexpected events, and responds to them, often by restructuring the genome' (McClintock, 1984). Here, once again, McClintock was 'ahead of her time', anticipating a conceptual shift not yet apparent to most others, one that needed to wait for the establishment of the science of genomics and the lessons to be learned from its analyses before becoming evident to mainstream geneticists. In short, a shift closely akin to that indicated by my title, *From gene action to reactive genomes* – a title that implies two dimensions in which focus has shifted: one from genes to genomes and the other, from action to reaction.

In the beginning

To better understand this shift, I want to turn to a very brief history of the Weismannian perspective in genetics, focusing on the definition of the subject of genetics and the forging of its language back in the earliest days of the field. I argue that a number of assumptions that seemed plausible at that time were built into the linguistic habits of geneticists geneticists. Those habits persisted throughout the 20th century, guiding our thinking about genetics and, at the same time, serving as vehicles of resistance to conceptual change. Primary among these have been the habits, first, of thinking of genomes simply as collections of genes, and relatedly, of confounding 'genes' as trait-makers with 'genes' as difference makers, i.e. with mutations.

Elsewhere. I have argued that the conceptual framework of classical genetics was dominated by what I call a discourse of 'gene action' – a discourse that grants both ontological and causal priority to those entities called 'genes', and accordingly, that fits well within the Weismannian perspective (see, e.g. Keller, 2000). For the paradigmatic school of T. H. Morgan, genetics was about tracking the transmission patterns of these entities. Even if no one could say what a gene was, it was assumed to be a unit, directly associated with a trait (a trait maker), and at the same time, a unit that could mutate, and through that mutation, could also be associated with the appearance of a difference in that trait (a difference maker), and hence mapped. But surely, genetics was meant to be more than the study of transmission patterns. As Willhelm Johannsen remarked early on, 'Is the whole of Mendelism perhaps nothing but an establishment of very many chromosomal irregularities, disturbances or diseases of enormously practical and theoretical importance but without deeper value for an understanding of the 'normal' constitution of natural biotypes?' (Johannsen, 1923: 140). Clearly not. Mapping 'difference makers' and tracking their assortment through reproduction may have been all that the techniques of classical genetics allowed for, but the aims of this new field were far larger. What made genes interesting in the first place was their presumed power

to mould and to form an organism's traits. Of course, the process by which genes exerted their power in the development of characters or traits was a total mystery, but the notion of gene action provided a crucial stop-gap. The hope was that the study of mutations would tell us how genes acted.

In retrospect it seems surprising how little effect the shift in focus from genes to DNA had on the discourse of gene action. To be sure, identifying the molecular structure of the 'gene' as a sequence of nucleotides went a long way in demystifying that concept, yet the central dogma managed to preserve the essential causal structure of the Weismannian framework (see, e.g. Griesemer & Wimsatt, 1989). Genes were now concrete material entities; protein makers rather than trait makers, carriers of the molecular information required to string together the sequence of amino acids to construct a poly-peptide. For the early architects of molecular biology, information referred to protein-coding sequences, DNA was made up of genes, and genes 'acted' by making proteins (Monod & Jacob, 1989).

However, even the efforts of Monod and Jacob to expand the 'purely structural' theory of genetics to include gene regulation left much of the basic picture intact. Their contribution was to add 'a new class of genetic elements, the regulator genes, which control the *rate* of synthesis of proteins, the *structure* of which is governed by *other* genes.' In their model, regulation was achieved through the presence of another gene (the regulator gene) coding for a protein that acts by repressing the transcription of the original structural gene. As they wrote, the discovery of regulator genes 'does not contradict the classical concept' (Monod & Jacob, 1961, p. 394). Even after the explicit incorporation of regulation, the genome could still be thought of as a collection of protein-coding sequences (genes), only now, some genes were purely structural, while others did the work of regulation. The central dogma still holds, genetic information is still located in protein-coding sequences, and the study of genetics is still the study of genes.

Over time, though, it became evident that there was far more DNA in the genome than could be accounted for by protein-coding sequences, but this 'extra' or 'non-genic' DNA was widely disregarded as being of little interest. Many referred to it as 'junk DNA'.

Enter genomics

I suggest that what finally dislodged the discourse of gene action has been the advent of genomics. As Francis Collins, director of the National Human Genome Research Institute, has written, 'The history of biology was forever altered . . . by the bold decision to launch a research program that would characterize in ultimate detail the complete set of genetic instructions of the human being' (Collins, 1999, p. 28). His words were prophetic, though perhaps not quite in the ways he imagined. Once the sequence of the human genome became available, it soon became evident that sequence information alone would not tell us 'who we are,' that sequence alone does not provide the 'complete set of genetic instructions of the human being'. In fact, many have commented on the lessons of humility that achievement brought home to molecular biologists. The genome is not the organism.

Indeed, genomic science has changed the very meaning of the term, turning the genome into an entity far richer, more complex, and more powerful – simultaneously both more and less – than the pre-genomic genome, in ways that require us to rework our understanding of the relation between genes, genomes and genetics. I want also to argue that it has turned conventional understanding of the basic role of the genome on its head, transforming it from an executive suite of directorial instructions into an exquisitely sensitive and reactive system that enables cells to regulate gene expression in response to their immediate environment, or, as McClintock (1984) anticipated, into a 'highly sensitive organ of the cell' that monitors [and regulates] genomic activities.

When the term was originally introduced in 1920 (see Keller, 2012, for a review of the term's usage), the genome was understood as the full ensemble of genes with which an organism is equipped, and that understanding continued to prevail throughout the 20th century. Even in the era of molecular biology, after the genome had been recast as the book of life, written in a script of nucleotides, it was not supposed that the instructions carried by the genome were uniformly distributed along the 3 billion bases of DNA. Rather, they were assumed to be concentrated in the units that 'contain the basic information about how a human body carries out its duties from conception until death,' i.e. our genes (Collins, 1999, p. 28). To be sure, it has become notoriously difficult to fix the meaning of the term gene, but, in practice, by far the most common usage refers, even to this day, to protein-coding sequences. Furthermore, as already indicated, it was in 1999 already well understood that our genes make up only a relatively small fraction of our genomes. As Collins wrote, these '80,000 or so human genes are scattered throughout the genome like stars in the galaxy, with genomic light-years of noncoding DNA in between.' But however vast, the 'noncoding DNA in between' was not the object of interest.

Indeed, the proposal to sequence the whole genome was initially met with considerable opposition. Bernard Davis, e.g. referred to the plan as 'blind sequencing', complaining that 'it would be necessary to plow through 1 to 2 million 'junk' bases before encountering an interesting sequence' (Davis, 1990). Similarly, Robert Weinberg (1991) wondered 'how useful most of this

information will be to anyone [since] upwards of 95% of our genome contains sequence blocks that seem to carry little if any biological information.' The primary focus of the Human Genome Project (HGP) was still, as it had been from its inception, on the genes, on compiling a comprehensive catalog of protein-coding sequences.

Collins predicted that the full sequence of the first human genome would be completed by 2003, and he anticipated it would produce a catalogue of roughly 80,000 genes. Other guesses ranged from 60,000 to 100,000. At the annual genome meeting held at Cold Spring Harbor the following spring (May 2000), an informal contest was set up in which researchers tried to guess just how many protein- coding sequences it takes to make a human. As Elizabeth Pennisi (2003, p. 1484) wrote, 'Some gene counters were insisting humans had upward of 100,000 genes, and just a handful were hinting that the number might be half that or fewer.'

Collins' estimate of the completion date was right on target. But by that time, many of the expectations informing the launching of the HGP had already begun to unravel. The first jolt came in June 2000 with the announcement of the first draft of the human genome, reporting a dramatically lower number of genes (~30,000) than had been expected. Since then, the count has tended steadily downward, settling by 2003 at somewhere between 20,000 and 25,000 – not very different from the number of genes in the lowly worm, *C. elegans*. Two questions became obvious: what, if not the number of genes, accounts for the vast increase in complexity between *C. elegans* and *Homo sapiens*? And second, what is the rest of the DNA for? Are we really justified in assuming that extra-genic DNA makes no contribution to function?

The existence of large amounts of extra-genic DNA was not exactly news, but its significance had clearly been muted by the assumption that it was non-functional. When the HGP was first launched, it was widely assumed that extra-genic DNA was 'junk', and need not to be taken into account. And indeed, it was not. But by the beginning of the new century, and largely in response to work associated with that project, a new metaphor began to make its appearance. Instead of 'junk', extra-genic DNA became the 'dark matter of the genome', with the clear implication that its exploration promised discoveries that would revolutionize biology just as the study of the dark matter of the universe had revolutionized cosmology.

This shift – from junk to dark matter – is in fact at the heart of my subject. It was identified in a 2003 article on 'The Unseen Genome' in *Scientific American*, where the author, W. Wayt Gibbs, wrote,

> Journals and conferences have been buzzing with new evidence that contradicts conventional notions that genes, those sections of DNA that encode proteins, are the sole mainspring of heredity and the complete blueprint for all life. Much as dark matter influences the fate of galaxies, dark parts of the genome exert control over the development and the distinctive traits of all organisms, from bacteria to humans. The genome is home to many more actors than just the protein-coding genes (Gibbs, 2003).

Of course, changes in conceptual frameworks do not occur overnight, nor do they proceed without controversy, and this case is no exception. The question of just how important non-protein-coding DNA is to development, evolution, or medical genetics remains under dispute. For biologists as for physicists, the term 'dark matter' remains a placeholder for ignorance. Yet reports echoing, updating, and augmenting Gibbs' brief summary are appearing in the literature with ever increasing frequency.

In 2003, the research consortium ENCODE (ENCyclopedia Of DNA Elements) was formed with the explicit mandate of identifying new function elements in the vast stretches (98.5–99%) of the human genome that is 'non-genic' – i.e. that does not code for protein. Early results (based on the analysis of 1% of the human genome) were reported in *Nature* in 2007 (ENCODE Project Consortium, 2007), and they effectively put the kibosh on the hypothesis that non-coding DNA lacked function (i.e. that it was junk, 'for' nothing but its own survival). They confirmed that the human genome is 'pervasively transcribed' even where non-coding; that regulatory sequences of the resulting ncRNA may overlap protein-coding sequences, or that they may be far removed from coding sequences; and finally, that non-coding sequences are often strongly conserved under evolution. Furthermore, they showed not only that non-coding DNA is extensively transcribed, but also that the transcripts are (now referred to as 'non-coding RNA' or 'ncRNA') are involved in many forms and levels of genetic regulation that had heretofore been unsuspected.

The reaction was swift. In his commentary accompanying the report, John Greally wrote,

> We usually think of the functional sequences in the genome solely in terms of genes, the sequences transcribed to messenger RNA to generate proteins. This perception is really the result of effective publicity by the genes, who take all of the credit (Greally, 2007, p. 783).

Since 2007, efforts have been directed towards understanding just how the various kinds of ncRNA transcripts function in regulation. To this end, the ENCODE project has been expanded to include the genomes of a number of model organisms (e.g. *C. elegans* and *D. melagonaster*), thereby making possible a comparative study of the relation between sequence and function (modENCODE Consortium, 2010). The more complete results were finally released in 2012, and to much fanfare. They were accompanied by a special issue of *Nature* (Sept. 6, 2012), a

new publicly accessible website, and extensive coverage in the lay press. While some additional protein-coding genes have now been identified, the principal results focus on regulation. In an early summary of the new findings, Mark Blaxter identified three interacting systems that coordinate gene expression in space and time:

> transcription factors that bind to DNA in promoters of genes, ncRNA that modifies gene expression post-translationally, and marking of the histone proteins on which the DNA is wound with chemical tags to define regions of the genome that are active or silent (Blaxter, 2010, p. 1758).

Of particular interest is the strong correlation between chromatin marks and gene expression (apparently mediated by ncRNA) and the high degree of connectivity between and among different regulatory systems that have now been found in all the model organisms studied (also mediated by ncRNA).

The take-home message would seem to be clear. Genetics is not just about genes and what they code for. It is also about how the DNA sequences that give rise to proteins are transcribed, spliced, and translated into amino acid sequences, in the appropriate amounts at the appropriate time and place; about how these, once assembled into proteins, navigate or are transported to the sites where, and when, they are needed; etc, etc. All of this requires coordination of an order of complexity only now beginning to be fully appreciated. It is also only now becoming evident that the ncRNA transcripts of the remaining 98–99% of the genome are central to this process.

These transcripts come in many sizes and are associated with a number of different mechanisms. Small RNA's can destabilize messenger RNA, influence the formation of chromatin and chromatin marks, and have even been linked to cancer. Now another class of ncRNA transcripts has been identified – 'large intervening noncoding RNAs' (or 'lincRNAs') – that can operate across long distances and may prove as important to cell function as protein-coding sequences (Pennisi, 2010). We have learned that ncRNAs are crucial to the regulation of transcription, alternative splicing, chromosome dynamics, epigenetic memory, and more. They are even implicated in the editing of other RNA transcripts, and of modulating the configuration of the regulatory networks these transcripts form (see, e.g. Mattick, 2004, 2010; Qureshi & Mehler, 2012). In short, ncRNA provides an immensely rich resource for a profusion of regulatory mechanisms that enable gene expression to respond to variations in both local and distal environmental context – they provide the means by which organisms can adapt to changing environments. Most of the modifications they give rise to are short term and more or less readily reversible, but they need not be. Those involved in development can persist for many generations of cell division; some can persist through generations. Unlike DNA, RNA sequences are malleable, routinely rewritten and reinscribed. But through reverse transcription, such changes can also come to be incorporated in the DNA, turning the genome itself into what Jim Shapiro calls a 'Read–Write' system (see, e.g. Shapiro, 2013). To be sure, the remarkable stability of genomic sequences – in good part itself a consequence of an immensely complex system of editing and repair – demands attention but it is far from inviolable. Nor, for that matter, need changes in DNA sequence be strictly random, independent of effect. Indeed, in view of the ingenuity we are seeing in RNA dynamics, it would be surprising if evolution had not given rise to some sort of mechanism of directed mutation. However, nothing in the argument for reconceptualizing the genome as a reactive system depends on this: the sophisticated mechanisms by which gene expression is regulated are quite sufficient to justify such a shift by themselves.

The post-genomic genome

The gap between a collection of protein-coding sequences and the full complement of genetic material (or DNA) of an organism is huge. Yet even so, and notwithstanding my earlier claims about the changes that have taken place in our understanding of the genome, that entity is still often regarded interchangeably as all of an organism's DNA, *or* as a collection of its genes, where the genes, the genome's constituent units, are assumed to be structurally impervious to environmental input. Despite all the changes the gene concept has undergone, many of even the most recent formulations retain the view of these entities (and hence of genomes) as effectively autonomous formal agents, containing the blueprint for an organism's life – i.e. all of the biological information needed to build and maintain a living organism. But I am claiming that current research in genomics leads to a different picture, and it does so by focusing attention on features that have been missing from our conceptual framework. In addition to providing information required for building and maintaining an organism, the genome also provides a vast amount of information enabling it to adapt and respond to the environment in which it finds itself. As indeed it must if the organism is to develop more or less normally, and to survive more or less adequately.

Today's genome, the post-genomic genome, looks more like an exquisitely sensitive reaction (or response) mechanism – a device for regulating the production of specific proteins in response to the constantly changing signals it receives from its environment – than it does the pre-genomic picture of the genome as a collection of genes initiating causal chains leading to the formation

of traits. The first job of the new genome is to detect the signals that impinge, and its second, to respond (e.g. by change in its conformation) in ways that alter the patterns of gene expression. Aeons of natural selection have ensured that the changes in gene expression patterns that result are appropriate to the new information, i.e. that they increase the long term survival of the organism. The signals impinging on the DNA come most immediately from its intra-cellular environment, but these, in turn, reflect input from the external environments of the cell and of the organism as a whole.

This reformulation gives rise to an obvious question: if the genome is so responsive to its environment, how is it that the developmental process is as reliable as it is? This is a question of major importance in biology, and it is rapidly becoming evident that the answer must be sought not only in the structural (sequence) stability of the genome, but also in the relative constancy of the environmental inputs, and, most importantly, in the dynamic stability of the system as a whole (see, e.g. Keller, 2000). Genomes are responsive, but far from infinitely so; the range of possible responses is severely constrained, both by the organizational dynamics of the system in which they are embedded and by their own structure.

Changes in DNA sequences (mutations) clearly deserve the attention we give them: they endure, they are passed on from one generation to the next – in a word, they are inherited. Even if not themselves genes, they are genetic. Some of these mutations may affect protein sequences, but far more commonly, what they alter is the organism's capacity to respond effectively to the environment in which the DNA finds itself, or to respond differentially to altered environments. This conclusion may be especially important in Medical Genomics where researchers routinely seek to correlate the occurrence of disease with sequence variations in the DNA. Since the sequences thus identified are rarely located within protein-coding regions of the DNA, the significance of such a correlation must lie elsewhere, i.e. in the regulatory functions of the associated non-genic DNA.

Mutations also provide the raw material for natural selection. But when we speak of Natural Selection as having programmed the human genome, I want to emphasize that it is precisely the capacities to respond and adapt for which Natural Selection has programmed the human genome. Like other organisms, human beings are reactive systems on every level at which they are capable of interacting: cultural, interpersonal, cellular, and even genetic. The reconceptualization of the genome that I propose (from agentic to reactive) allows us – indeed obliges us – to abandon many of the dichotomies that have driven so much fruitless debate, for so many decades. If much of what the genome 'does' is to respond to signals from its environment, then the bifurcation of developmental influences into the categories of genetic and environmental, or nature and nurture, makes no sense. Similarly, if we understand the term environment as including cultural dynamics, perhaps neither does the division of biological from cultural factors. We have long understood that organisms interact with their environments, that interactions between genetics and environment, between biology and culture, are crucial to making us what we are. What research in genomics shows is that, at every level, biology itself is constituted by those interactions – even at the level of genetics. Returning to Weismann's view that the idea of inheritance of acquired characteristics is like 'supposing that an English telegram to China is there received in the Chinese language' (Weismann 1904, p. 63), I might suggest that a metaphor better fitting biological reality might even reverse the roles of sender and receiver, supposing a telegram sent from China that, if it was to be read, required its German readers to learn Chinese.

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